Remarks

Favorable consideration of this application is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 1-12 and 14-20 are pending in the application. Claims 1-12 and 14-20 have been rejected. Claims 1, 5, 7-11, and 16-20 have been amended, support for which can be found within the present application. No new matter has been added.

Claim Objections

The Examiner objects to claim 1 and dependent claim 11 because the preamble of claim 1 is inconsistent with the bodies of the claims. Applicants have modified claims 1 and 11 to include "mammalian," thus reconciling the perceived inconsistencies between the preamble of claim 1 and the bodies of those claims. No new matter has been added.

Rejection Under 35 USC §112, Second Paragraph

Claims 1, 16, and 20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. In particular, the Examiner has expressed confusion over the use of "undesired" isoforms in claims 1 and 20. Without acquiescing to the Examiner's rejection, Applicants have amended claims 1 and 20 to replace the terms "desired" and "undesired" with "specific" and "other," respectively. Both "desired" and "specific" denote an isoform of interest to the practitioner, as opposed to "undesired" or "other" isoforms not of interest. This is clearly explained and supported within the present specification, and furthermore, the concept of isolating a gene, protein, or other reagent of interest relative to (e.g., to the exclusion of) similar genes, proteins, or reagents (in this case, isolating an isoform of interest by excluding other isoforms) is well known in the present field of art.

The Examiner has indicated that claim 16 lacks clarity regarding whether said endogenous promoter is present in an expression vector containing said desired isoform. Without acquiescing to the Examiner's rejection, Applicants have amended claim 16 to include "using a knock-in construct." No new matter has been added, and support for amended claim 16 can be found at least at page 13, line 5 of the present specification.

Rejection Under 35 USC §112, First Paragraph- Written Description

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner states the following about claim 1:

> As such, claim 1 requires knowledge of a sizable number of isoforms of any gene products that may be expressed as multiple isoforms, in order to determine which isoforms of a gene product would be considered undesired. Further, the claim requires knowledge of numerous desired isoforms of a gene product, whether endogenous to said cell or isoforms that may be exogenous in origin. Knowledge of numerous isoforms would also be required to determine the nature of the sequences that would constitute a common and shared nucleic acid.

As the Examiner is aware, the USPTO carries the initial burden of establishing why a person skilled in the art would not recognize that the written description provides support for the claims, and there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. (MPEP § 2163)(*In re Wertheim*, 541 F.2d 257, 263)(66 Fed. Reg. 1099 (January 5, 2001)). For at least the following reasons, Applicants believe this burden has not been met, and therefore respectfully request the withdrawal of the present rejection.

I. The Present Application Provides Adequate Written Description Support for the Elements and Steps of the Present Method Claims

Applicants respectfully disagree with the above-cited statement by the Examiner, in particular with the assertion that "[...] claim 1 requires knowledge of a sizablenumber of isoforms *of any gene products that may be expressed as multiple isoforms*, in order to determine which isoforms of a gene product would be considered undesired" (emphasis added). Applicants also respectfully disagree with the Examiner's comment of the same nature, at page 4, line 24 of the present Office Action, that "the specification provides no description *of the substantial number of genes that can express more than one isoform, as claimed in claims 1 and 20*" (emphasis added). Consistent with these statements are the Examiner's request for the provision of "adequate description of such core structure and function related to that core structure," and assertion that "an Artisan of skill would not recognize from the disclosure that Applicant was in possession of *the genus of numerous genes and gene products that may give rise to or be described as isoforms*" (emphasis added).

These statements, and all of the arguments raised by the Examiner on page 5 of the present Office Action, appear to posit that the claims of the present invention require knowledge of every possible isoform of every gene product that is capable of expression via multiple isoforms. This is certainly not the case, and the present claims in fact only require a limited degree of knowledge on the part of the average practitioner.

It is important to point out that the claims of the present invention are method claims, and as such, the written description support which the present specification must provide *regards the steps and elements of the claimed methods*. Applicants respectfully believe the Examiner to be in error in his request for proof of adequacy of written description support *for an entire genus of*

genes or gene families (as described at least on page 5 of the present Office Action). These are not composition of matter claims that purport to claim an entire class of genes, and as such, written description support is required only for the steps and elements of the claimed methods. The steps and elements of the claimed methods are indeed supported vis-à-vis written description by the present specification.

As support for the above, Applicants point to Example 18 of the USPTO's "Revised Interim Written Description Guidelines Training Materials," which can be found at http://www.uspto.gov/web/offices/pac/writtendesc.pdf. Example 18 describes a process claim where the novelty is in the method steps, as is the case with present claims 1-12 and 14-20. Example 18 lists claim 1 as "A method of producing a protein of interest" that comprises steps for producing proteins using mitochondria from the fungus *Neurospora crassa*. As critically stated in the Analysis portion of Example 18, "A particular nucleic acid is not essential to the claimed invention." In the same way, a particular gene product is not essential to present method claims 1-12 and 14-20, whereas adequate description of the steps and elements of the methods is essential (and present).

As the Examiner describes in the present Office Action (citing the January 5, 2001 Federal Register and MPEP § 2163), the provision of adequate written description support can be accomplished by "showing that the invention was 'ready for patenting,' or by describing distinguishing characteristics sufficient to show that Applicant was in possession of the claimed invention." In the case of the present method claims of the invention, Applicants have provided support for the steps and elements at least at page 10, line 27 of the present specification (support is provided for, among other things, an "isoform" of a gene product of interest, cells to use for expression of the gene product of interest, expression vectors to use, etc.).

II. Practitioner of the Present Method Claims Only Requires Knowledge Related to Her Gene Product of Interest

Applicants reiterate that, for a variety of reasons, the present claims do not require knowledge of every possible isoform of every gene product that is capable of expression via multiple isoforms. In fact, a practitioner of the present method claims only requires knowledge *related to her gene product of interest*. By way of example, if a person of ordinary skill in the art is interested in isolating an isoform of hypothetical Gene A, she only need possess a working knowledge of two or more isoforms of Gene A; knowledge of other gene products would be superfluous. As demonstrated in the Examples beginning on page 17 of the present invention, in order to isolate knock-down or inhibit a specific isoform of the ShcA gene, the practitioner only required knowledge of the three isoforms of ShcA, all of which is readily available in the literature. A quick search for information about ShcA on the NIH's National Center for

Biotechnology Information (NCBI)(http://www.ncbi.nlm.nih.gov), for instance, reveals information about that gene's three isoforms.

See, for example, the OMIM (Online Mendelian Inheritance in Man) entry for ShcA (# 600560, at (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600560)), which clearly lists isoforms p46, p52, and p66 at the top of the page. That record also provides links to the GenBank records and nucleotide sequences for each isoform. Anything else required by a practitioner who wishes to employ the claims of the invention to isolate isoforms of SchA (e.g., a determination of regions of overlap necessary for the development of anti-schA siRNAs, cells in which SchA can be expressed, etc.) can easily be deduced from the readily-available knowledge of the isoforms of ShcA. For instance, performing a simple multiple-sequence alignment with the three known isoforms of ShcA reveals to the average practitioner areas of sequence overlap that can be used to develop the inhibitory nucleotides of the invention.

In the same way that Applicants compiled data about ShcA for the Examples section of the present application, a person of ordinary skill in the art can cull information for her gene product of interest. Said practitioner, who presumably already knows about her gene product of interest (in order for it to be "of interest," "desired," or otherwise worth investigating), can easily find bioinformatics data from a wide variety of publicly-available and/or for-purchase sequence databases, the use of all of which is routine. The NCBI website, for example (http://www.ncbi.nlm.nih.gov), contains well-annotated records for an enormous number of sequences, *including about the sequence isoforms, splice variants, alternative transcriptional and translational start sites.* Searching for the word "isoform" within the NCBI's nucleotide database, for instance, reveals over 170,000 hits. Literature searches similarly reveal isoform information about gene products of interest to a person of ordinary skill in the art, empowering her to employ the claims of the invention without difficulty.

Applicants list in at least the first paragraph of page 11 of the present application a wide variety of classes of gene products of interest, all of which exist in various isoforms and which are amenable to the method claims of the present invention. Non-limiting examples of therapeutically important proteins that can easily be used with the methods of the present invention include enzymes, e.g., kinases (PKB), ras, integrins, E2F, Rb, FGF, other signaling molecules and transcription factors.

Applicants also respectfully disagree with the Examiner's statement that "[f]urther, the claim requires knowledge of numerous desired isoforms of a gene product, whether endogenous to said cell or isoforms that may be exogenous in origin. Knowledge of numerous isoforms would also be required to determine the nature of the sequences that would constitute a common and shared nucleic acid." As stated above, information about the different isoforms of a gene product of interest should be readily available to, and easily acquired by, a person of

ordinary skill in the art. However, even if there exist previously unforeseen or uncharacterized isoforms, they can easily be determined practicing routine techniques known in the art.

An ordinary practitioner can, for instance, screen a cDNA library known to express the gene of interest, using probes generated from one or more of the known isoforms. The cDNA hits generated from the library should correspond to the plenary set of mRNA transcripts for the gene of interest, *including all its isoforms, splice variants, etc.* Pulling the cDNA clones, sequencing them, and analyzing them using bioinformatics techniques, gives rise to sufficient information about the various isoforms of a gene of interest to practice the method claims of the present invention. All of these techniques, although potentially time-consuming, are routine in the field of molecular biology and biotechnology, and should be familiar to the ordinary practitioner. Applicants therefore posit that a practitioner of the claims of the present invention possesses enough information about the isoforms of her gene product of interest to require nothing further of the claims of the invention (and certainly nothing beyond the scope of what is customarily researched in the field).

Rejection Under 35 USC §112, First Paragraph- Enablement

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. In particular, the Examiner states:

> [T]he specification, while being enabling for a method expressing a desired isoform of the Shc gene product in a mammalian cell *in vitro*, following suppression of the expression of the undesired isoforms of said gene product, by contacting said cell with ds RNA, does not reasonably provide an enablement for a method of expressing a desired isoform of *any gene product* in a cell absent undesired isoforms of *any gene product* (claims 1 and 20), by exposing said cell to dsRNA, and wherein said cell is a cancer cell (claim 14), as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims (emphasis added).

Applicants thank the Examiner for recognizing the enablement of at least a portion of the present invention, and respectfully posit that the Examiner should similarly recognize the enablement of the remainder of the claimed invention, for at least the following reasons.

As discussed above in regard to the written description rejection, Applicants respectfully believe the Examiner to be in error in his assertion that the method claims of the present invention require knowledge of every possible isoform of every gene product that is capable of expression via multiple isoforms. Again, this is not the case, and therefore, the arguments employed above for the written description rejections are apposite for enablement as well- i.e., Applicants only need to demonstrate support (in this case, evidence of enablement) for the steps and elements of the present method claims, and not for the complete set of every possible isoform of every gene product that is capable of expression via multiple isoforms.

On page 9 of the present Office Action, the Examiner cites the Caplen et al. reference (Gene 2000, vol. 252, p. 95-105) and states, "The unpredictability of attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi) is evident in prior and post-filing art. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable."

Applicants respectfully offer the following references (summaries of which are given) in an effort to show that the field of RNA interference is more predictable and reliable than the Examiner describes. These references describe the use of inhibitory RNAi sequences to:

- Silence cancer-associated genes *in vitro*, including K-RAS (Brummelkamp et al. (2003) Nat. Rev. Cancer 3:781-9), HPV16, and bcr-abl (Scherr et al. (2003) Blood 1011:1566-9), and inhibit tumor formation *in vivo*.
- Ameliorate the symptoms of Severe Acute Respiratory Syndrome (SARS) in Rhesus monkeys (Li et al. (2005) Nat. Med. 11:944-51).
- Block the expression and replication of Hepatitis C (HCV) virus in human hepatoma cell lines (Wilson et al. (2003) Proc. Natl. Acad. Sci. USA 100:2783-8).
- Suppress the growth of human papillomavirus positive cancer cells *in vitro* and *in vivo* (Yoshinouchi et al. (2003) Mol. Ther. 8:762-8).

For the reasons stated above, Applicants respectfully request withdrawal of the enablement rejection of claims 1-12 and 14-20.

Rejection Under 35 USC §102(e)

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §102(e), as anticipated by Tuschl et al. (U.S. Patent Publn. No.: 2004/0259247)(hereafter, "the Tuschl reference"). Although the Tuschl reference and the claims of the present invention are similar in that both pertain to RNAi, Applicants respectfully disagree that the Tuschl reference anticipates the present claims. In fact, Applicants cite Tuschl publications related to the Tuschl patent application reference in the present application, as a way of describing past contributions to the RNAi field before distinguishing the present methods of the invention from any of the Tuschl work described. Applicants recognize that not every element of claims 1-12 and 14-20 is met by the Tuschl reference, and therefore respectfully request withdrawal of the §102(e) rejection.

The RNAi methods disclosed in the Tuschl reference are used for knocking out a target gene of interest and, in some cases, providing a replacement copy. In preferred embodiments (as described at least in paragraph [0040]), Tuschl combines knocking out a target gene of interest with the provision of a replacement copy gene, or a "knockout and rescue" methodology; this is "particularly suitable for identifying functional domains of the target protein." Said

techniques are akin to "gene targeting" methods of inducing homologous recombination seen in the transgenic animal field.

The present invention, on the other hand, provides methods of isolating isoforms of interest of gene products of interest, to, e.g., evaluate gene function as it relates to the existence of multiple isoforms. The present methods allow for the study of proteins of related sequence but with biochemically and/or biologically distinct features, something not possible employing the Tuschl methodology. The present methods are unique and do not have an analogy in the transgenic animal field.

For purposes of the present analysis, and without acquiescing to the Examiner's §102(e) rejection or any components thereof, Applicants will temporarily assume that the Examiner has accurately described an analogy between the use of "exogenous" and "endogenous" in Tuschl and "desired" and "undesired" in the present method claims (as formerly used (now "specific" and "other")), respectively. The Tuschl reference describes using RNAi to inhibit the expression of endogenous target genes, thereby knocking them out (i.e., suppressing their function); on the other hand, the present invention contemplates inhibiting isoforms of a gene of interest, while protecting isoforms of interest of the gene of interest. Critically, the latter allows for the investigation of the function of individual gene isoforms, while the former does not.

Applicants respectfully request entry of the amendments to the claims and the specification and submit no new matter is added thereby. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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